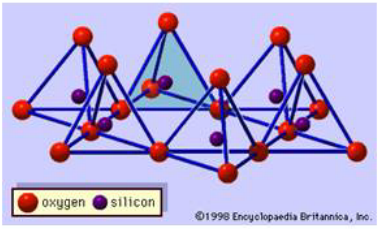
NTP
National Toxicology Program

Silica Flour
(Finely Ground Crystalline Silica)

Concept Review

December 9-10, 2009



Nomination

- Silica Flour was nominated by a private individual for toxicological testing via oral and dermal exposure with emphasis on immunotoxicity testing
  - Occupational exposure to silica is linked to higher rates of autoimmune diseases such as lupus, rheumatoid arthritis, and scleroderma
  - The nominator suggested human exposure might be via cosmetic products and filler in vitamins and pain relievers
  - Paucity of oral and dermal toxicity data on silica flour
- Most data on silica is based on respiratory exposure
- Occupational exposure to respirable crystalline silica is known to cause silicosis and to be carcinogenic

Forms of Silica (Silicon Dioxide, SiO_2)

- Types of Silica
  - Amorphous silica - no crystalline structure
  - Synthetic amorphous silica - manmade using wet or thermal process
  - Crystalline silica - (quartz, cristobalite, tridymite)
    - Range of particle sizes
- Silica flour: finely ground quartz crystals
  - 1-100 µm
  - Extremely pure
  - Consistency of flour

Use

- Abrasive cleaner and inert filler
  - Scouring powder, metal polish, toothpaste (?)
  - Glass, ceramic and tile production
  - Extender in paint; a component in road surfacing material
  - Skin care products including exfoliants, scar and acne treatments, corn/callus and wart removers
  - Mineral-based cosmetics, and hair-and nail-care products
- Not noted as an ingredient in OTC pharmaceuticals
  - Two major brands pain reliever tablets: colloidal silicon dioxide (amorphous)
  - Three major brands multivitamin pills: non-crystalline silica

Human Health Effects

- Occupational exposure to respirable crystalline silica in the form of quartz or crystobalite is a known lung carcinogen (IARC 1997)
- Numerous occupational epidemiology studies reported moderately elevated risk for extrapulmonary cancers including the GI tract
- Inhalation of respirable crystalline silica associated with chronic silicosis, usually a nodular pulmonary fibrosis
- Other silica-related diseases include pulmonary tuberculosis, chronic obstructive pulmonary disease, chronic renal disease, hyperthyroidism, scleroderma, rheumatoid arthritis and lupus

Animal Toxicity Studies: Non-Respiratory Exposure

- Subcutaneous injection: Silica flour (<5 μm) induced hepatic fibrosis and granulomas in nude mice and hamsters
- IV injection: Adjuvant effect on antibody production
- Oral exposure: Exposure of guinea pigs to crushed quartz in drinking water for 4 months caused focal tubulo-interstitial nephritis
- Oral exposure: Acute exposure of mice to nanoscale silica (10-20 nm) induced non-specific focal hemorrhage in liver and heart
- Oral exposure: Mice fed nanoscale silica (30 nm) for 10 weeks had fatty liver and increased ALT
- Dermal exposure: No toxicity data found

ADME

- Few ADME data relevant to non-respiratory exposure
  - Limited studies suggest oral bioavailability

Key Issues

- General lack of oral or dermal toxicity data
- Lack of ADME studies via non-respiratory routes
- For most appropriate selection of test material for study, need a better understanding of particle size, shape and other physical/chemical characteristics in consumer products

Proposed Approach and Specific Aims

- Better define potential exposure
  - Define particle characteristics in various consumer products containing crystalline silica to choose appropriate test material
- ADME
  - Conduct ADME studies to determine bioavailability if feasible
    - Oral exposure studies before dermal exposure
    - Conduct studies using particles of 2 or 3 size ranges/shapes if warranted
      - Collect samples for immuno screening
    - Investigate if there is a particle size/shape factor in bioavailability
- Immunotoxicity
  - Conduct immunology assays using the NTP tiered testing panel. Select clinically appropriate autoimmune animal model based on effects.
- General toxicity
  - Consider conducting general toxicity studies based on above findings

Significance and Expected Outcomes

- NTP studies on silica flour would
  - Investigate potential for oral exposure to crystalline silica to cause non-pulmonary adverse effects including autoimmune disease
  - Provide ADME data
- Currently there is a data gap for the potential toxicity of non-respiratory exposure to crystalline silica
  - NTP research program would address this data gap

Questions?